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SANTANGELO LAW OFFICES, P.C.
125 SOUTH HOWES, THIRD FLOOR
FORT COLLINS, CO 80521

EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,809	SEIDEL ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 1/20/05.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,5-12,16,17,19-29,165-167,169,170,172-183 and 185 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,5-12,16,17,19-29,165-167,169,170,172-183 and 185 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HL

DETAILED ACTION

1. This action is in response to the amendment filed January 20, 2005. Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 are now pending. Claims 2-4, 13-15, 18, 30-164, 168, 171, and 184 have been cancelled. Applicants arguments and amendments have been fully considered, but are not persuasive to overcome all previous grounds of rejection. Any rejections not reiterated herein are hereby withdrawn. This action is made final.

Applicants response requests an opportunity for an interview "in the event questions remain." If Applicants would like an interview to discuss this application, then Applicants should contact the examiner to schedule an interview.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing bovine offspring wherein the methods comprise collecting semen from a bovine, staining the sperm cells in the semen, sorting the sperm by sex chromosomes using a MoFlo flow cytometer / cell sorter at 50 psi using 2.9% Na Citrate as a sheath fluid, collecting the sperm at approximately 500 live sperm/second into tubes containing Cornell Universal Extender (CEU) with 20% egg yolk, and using, within 5-9 hours post-sorting, 3×10^5 live, cooled sperm to inseminate

bovine that were previously synchronized with prostaglandin F-2 alpha at 12 day intervals, wherein said method results in pregnancy rates of about 80% of controls inseminated using 15.6 X 10^6 motile non-sorted/unsexed sperm (see page 25 of the specification, does not reasonably provide enablement for methods of producing any nonhuman mammal wherein said methods comprise sensing a sex characteristic of sperm cells, sorting sperm cells by any means based on the sex characteristic, generating an insemination sample having a low number of sperm capable of fertilizing at least one egg within a female at success levels comparable to a typical insemination dosage, inserting any portion of the insemination sample into the female, fertilizing at least one egg within the female and producing a nonhuman offspring mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are broadly drawn to for methods of producing any nonhuman mammal wherein said methods comprise sensing a sex characteristic of sperm cells, sorting sperm cells by any means based on the sex characteristic, generating an

insemination sample having a low number of sperm capable of fertilizing at least one egg within a female at success levels comparable to a typical insemination dosage, inserting any portion of the insemination sample into the female, fertilizing at least one egg within the female and producing a nonhuman offspring mammal. The claims in general do not define the step of sensing the sex characteristic or separating the sperm. The claims do not set forth how the sex characteristic is "sensed" and do not set forth the conditions or instrumentation used for separating the sperm cells based upon the sex characteristic. It is noted that the claims recite using a percentage of a typical insemination sample. But do not recite the actual amount of sperm used for insemination since the claims allow for using any portion of this sample to inseminate a female nonhuman mammal. It is unclear as to what portion of the sample would be used in the insemination process and in view of the comprising language, it is unclear as to whether additional undefined samples may also be used for the insemination process. The claims further include methods in which insemination occurs 12 hours after the time that is generally regarded as optimal for a single insemination (claims 10 and 174); methods in which insemination occurs up to 17 hours or later than about 10 hours after the insemination sample is established (claims 11 and 176, respectively); methods in which the sperm cells are separated at a rate of at least 1200 sorts per second; and methods in which the insemination sample contains at least 60%, 70%, 80% or 90% of sperm having the desired sex characteristic (claims 172, 173, 182 and 183).

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed

invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, specification has not adequately taught one of skill in the art how to practice methods of producing any nonhuman mammal using a low number of sorted sperm and achieving success rates comparable to that obtained with a "typical insemination dosage" for the following reasons.

The claims broadly encompass methods for producing any nonhuman mammal using a low number of separated sperm while still achieving success rates comparable to that obtained with a typical insemination sample. However, the specification provides only one specific example in which such a method has been accomplished. In particular, example 1, set forth on 25 of the specification, describes a method of using a "low dose" of sex sorted sperm for artificial insemination of a bovine. The method requires collecting a sperm sample from a bovine, staining the sperm cells in the semen, sorting the sperm by sex chromosomes using a MoFlo flow cytometer / cell sorter at 50 psi using 2.9% Na Citrate as a sheath fluid, collecting the sperm at approximately 500 live sperm/second into tubes containing Cornell Universal Extender (CEU) with 20% egg yolk, cooling the sperm sample, and using 3×10^5 live, cooled

sperm to inseminate bovine that were previously synchronized with prostaglandin F-2 alpha at 12 day intervals. The sorted sperm were used for insemination within 5-9 hours after sorting and the method resulted in pregnancy rates of about 80% of controls inseminated using 15.6 X 10^6 motile non-sorted/unsexed sperm. Example 3 of the specification also describes a method of using sex-sorted, unfrozen sperm for insemination purposes. This example states that in one instance insemination with 1-2 X10^5 sperm in .1 ml resulted in pregnancy rates of 41% at 8 weeks and in pregnancy rates of 50% at 8 weeks when insemination was performed within 10 hours of the end of sorting.

The specification clearly sets forth the unpredictability in the art of using sex sorted sperm for artificial insemination and particularly of using low-dosages of sex sorted sperm for AI. There are an extensive number of variables which effect the viability of the sperm, the success rate of AI and the pregnancy success rate. For example, at page 3, the specification states that "the sperm are time-critical cells. They lose their effectiveness the longer they remain unused." In Example 3, the specification teaches that when 38 heifers were inseminated about 22 hours post-sorting, none of the heifers were pregnant 8 weeks after insemination. When inseminations were done 18-29 hours post-sorting, of 33 heifers only 1 remained pregnant at 8 weeks. Additionally, when inseminations were performed 17 to 24 hours post-sorting, only 1 of 7 inseminated females was pregnant at 8 weeks. Accordingly, it is highly unpredictable as to whether sorted bovine sperm samples can be used at time periods of more than 10 or at periods of 17 or more hours post-sorting and still allow for success rates

comparable to those obtained with typical inseminations. The specification also emphasizes the unpredictability of using low dosage sex sorted sperm for insemination. The specification defines "low dose" as including levels of 10% to 50% of typical, non-sorted insemination samples. However, the specification exemplifies using low dosages of sex sorted sperm only with bovine animals wherein the dosage is a minimum of 1-3 x 10^5 live, cooled sperm used within 10 hours of sorting. Given the unpredictability in using low dosages of sex sorted sperm for insemination purposes, it is highly unpredictable as to the quantity of bovine sperm or other mammalian sperm that would acceptable to allow for fertilization success rates comparable to those obtained with high dosages of unsorted semen.

The specification (at page 27) also teaches that the handling of the sample post-sorting significantly effects the success of the insemination process. When insemination samples were shipped at ambient temperature, 0 out of 10 females became pregnant. Only when the sperm was cooled to 5C during shipping, was insemination effective.

At page 3-4, the specification discusses additional factors which prevent the hinder the use of sex-sorted sperm. It is stated that "the process through normal flow cytometer techniques may, in fact, be unacceptable for cytometric sorting of sperm cells in certain applications. The sensitivities range from dilution problems and the flow cytometers inherent need to isolate and distinguish each cell individually as well as the pressure sand other stresses which typical flow cytometry has, prior to the present invention imposed upon the cells or other substances that it was sorting. This may also represent a unique factor for sperm cells because it appears that even though the

sperm cell may appear to pass through the flow cytometer and be sorted with no visually discernable side-effects, in fact, the cells themselves may have been stressed to the point that they perform less optimally in the insemination process." While this passage appears to state that these problems occurred only prior to the present invention, the specification and claims do not recite any particular advancements which allow for the ordinary artisan to overcome each of these problems when sorting sex from any organism, using any means for sensing a sex characteristic, any means for separating the sperm, any means for collecting the sperm, any means for storing and transporting the sperm, any low dosage of sperm and any means of artificial insemination. The specification teaches that the sorting rate and pressure used to run the flow cytometer may significantly effect sperm viability. However, the majority of the claims allow for the use of any type of apparatus to sense the sex characteristic and to separate the sperm cells based on the sex characteristic. The specification does not provide sufficient guidance to enable the skilled artisan to use any apparatus under any conditions, and particularly under any conditions of pressure or sort rate, to generate insemination samples that achieve fertilization rates comparable to those obtained with unsexed, unsorted sperm cells.

The specification further teaches that the selection of a sheath fluid greatly influences the viability of the sperm cells. For instance, at page 12, the specification teaches that "the stress imposed by handling of the cells within the flow cytometer appears significant for this application...For instance, while it has been known to utilize fluids having a proper pH factor or osmoality, the present invention recognizes that

there may be certain chemical compositions to which the cells may be hyper-responsive. These hyper-responsive chemical compositions may naturally vary based upon the cells or even the prior handling of the cells." The specification goes on to teach a specific citrate-based sheath fluid for sorting bovine cells and a HEPES-based sheath fluid for sorting equine cells. However, the specification does not teach chemical compositions that are suitable for sorting other types of mammalian sperm. As set forth in the specification, a sperm cells response to a chemical will vary depending on the type of chemical, source of sperm cell and previous handling of the sperm cells. The identity of the chemicals that cause stress to sperm cells from other bovine, equine and other mammals can only be determined through experimentation. There is no predictable means for determining a priori which sheath fluids will impose minimal stress on the sperm cells and allow for the sorting of sperm cells to generate an insemination sample that can be used to fertilize eggs at the same success level as a typical insemination sample. In particular, with respect to claims 27 and 177, the specification has not enabled using any HEPES sheath fluid for the sorting of any type of sperm cell. The specification has stated that it is unexpected that HEPES-based HBGM3 solution was effective as a sheath fluid during the sorting of equine sperm. The specification has not taught that this solution can be used with other sperm cells or that other HEPES solutions can be used with equine or other types of sperm cells. In view of the unpredictable effects that chemical compositions may have on the viability of sperm cells, undue experimentation would be required to practice the methods of claims 27 and 177 as they are broadly claimed.

Other factors which influence sperm viability include different aspects of the collection process. At page 15, the specification teaches that "it may be important that the container which makes up the collector be properly sized so that it acts as some means of avoiding an impact between the cells and the container itself." The specification also discusses the criticality of selecting a proper collection fluid in order to reduce stress to the sperm cells.

The specification further teaches that the dilution process may effect the success rate of the insemination process. At page 21 of the specification, it is stated that "It has been discovered that dilution may create an effect upon the sperm cell's viability and so it may be appropriate to avoid too large a level of dilution by providing a smaller sample." However, the specification does not teach what would constitute an appropriate level of dilution or appropriate type of dilution solution for diluting the sperm of the wide array of non-bovine mammals encompassed by the claims and does not provide sufficient guidance for selecting alternative dilution levels and solutions for non-bovine sperm samples. The unpredictability surrounding the insemination process is highlighted by the passage at page 22: "The utilization of embryo transfer equipment may be used because there may be high sensitivity of the uterine wall for such low dose, sexed inseminations." Yet, the specification does not clarify which mammals require or do not require the utilization of embryo transfer equipment.

With respect to claim 23, the step of staining the sperm cells is also known to be critical in influencing the viability of the sperm and effectiveness of the sorting procedure to obtain viable sperm. Responsiveness to stain also varies depending on the type of

stain. The specification (page 20) teaches that higher amounts of stain might "to some extent" provide better results. The specification teaches using a solution of 38uM Hoeschst 33342 stain. The specification does not specifically exemplify improved results using this concentration of stain. Claim 23 allows for the use of any stain, as long as it is present at a concentration of 38uM. However, the specification does not teach any stains other than Hoeschst 3342 that can be used at this concentration. In view of the unpredictability as to how a stain and the concentration of stain will effect the viability of sperm cells and the sorting process, undue experimentation would be required to practice the claimed invention using any stain at a concentration of 38uM.

Additionally, the ability to apply the claimed sorting and insemination method to non-bovine mammals is highly unpredictable. The specification does not provide any specific examples of using low doses of sex sorted sperm for insemination in non-bovine animals. Given the variability in sperm viability in different species and the variability in sorting success and insemination success in different species, it is highly unpredictable as to whether the results obtained with bovine can be extended to other species. The unpredictability in applying the claimed invention to non-bovine mammals is emphasized by the teachings in the specification. At page 4, the specification states that "artificial insemination with a high success rate is one of a statistical nature in which a multitude of factors seem to interplay. Thus, solutions proposed to some degree involve a combination of factors which, when thoroughly statistically studied, will be shown to be necessary either in isolation or in combination with other factors. Such a determination is further compounded by the fact that **the results vary by species** and

may be difficult to ascertain due to the fact that testing and statistical sampling on a large enough database is not likely to be worth the effort at the initial stages." Yet, the specification does not provide any specific guidance as to what particular combination of factors/conditions would be required to obtain comparable success rates in non-bovine, non-human mammals. Additionally, the teachings of Johnson (cited in the IDS; Journal of Reproduction and Fertility, 1997) highlight the unpredictability of using low dosage sex sorted sperm in other mammals. Specifically, Johnson (page 262) teaches that "It is unlikely that the technology for small numbers of spermatozoa from cattle will be directly applied to swine because of the anatomy of the pig uterus which provides an impediment to small numbers of spermatozoa." The specification does not particularly address this limitation and does not provide any particular guidance as to how to overcome this obstacle when inseminating pigs or other mammals having a uterus of similar anatomy. Furthermore, Cran (Theriogenology, January 1997) also emphasizes the unpredictability of using low doses and/or sex sorted semen for insemination. Cran teaches that pregnancy rates of lambs were low when sex sorted semen was used for insemination. In one study, 0 of 18 ewes inseminated with low doses of X sperm lambed, while 5/12 inseminated with unsorted sperm produced lambs. In a second study, none of 5 ewes inseminated with low dose Y sperm lambed; 4/25 inseminated with low dose X sperm lambed; and 2/30 inseminated with unsorted low dose sperm lambed. Cran states that the low pregnancy rates may be due to a combination of delay between semen collection and insemination, asynchrony between insemination and ovulation, semen doe and the onset of seasonal anestrus. However, the specification

and prior art do not provide any specific guidance as to how to modify the method of Cran so as to predictably generate a method in which low doses of ram semen can be used to produce fertilization rates equivalent to that obtained when using high doses of unsexed sperm. It is unpredictable as to how the methodology would need to be modified in order to effectively perform low dosage AI with sex sorted sperm in other mammals, including elephants, whales, gorillas, pandas etc. The teachings in the specification regarding bovine do not provide sufficient guidance to enable the use of this technology in other mammals because it is unclear as to how the viability of the sperm will be effected by the rate and pressure of the sorting process, the sheath fluid used for the sorting process, the collection fluid and collection container, the dilution process, the freezing process, and the type of insemination procedure.

Accordingly, the specification emphasizes the unpredictability in the art of using low dose sex-sorted sperm for AI and teaches that a multitude of factors interact in undefined ways to influence the viability of the sorted sperm and the success rate of insemination. However, the specification teaches only one particular set of conditions – i.e., the conditions set forth in Example 1 - that were shown to be effective for achieving success rates with low dose sex-sorted sperm comparable to success rates achieved using a typical high dosage, nonsorted insemination sample. Sufficient guidance is not provided in the specification as to how to modify the conditions set forth in Example 1 and maintain a success rate that is about 80% of the success rate achieved with typical insemination samples. Additionally, sufficient guidance is not provided in the specification as to how to apply the methodology used with bovine to all other non-

human mammals. The genus of non-human mammals is significantly large and includes a vast multitude of animals whose sperm has not been previously studied for its ability to be sorted, for its sensitivity to chemicals and the sorting process, for its sensitivity to handling and freezing processes or for its ability to be used for insemination purposes. Accordingly, extensive experimentation would be required to practice the claimed invention using other sorting and insemination conditions for bovine sperm or using sperm from non-bovine, non-human mammals.

With respect to claims 172, 173, 182 and 183, the specification does not reasonably provide enablement for methods of producing any non-human mammal using an insemination sample having a plurality of spermatozoa wherein up to 100% of the spermatozoa have the same sex determination characteristic. The ability to sort sperm from any nonhuman mammal on the basis of a sex determination characteristic such that the resulting sample can be used for fertilization to reproducibly generate offspring in which 90% of more of the offspring are female is highly unpredictable. This unpredictably is exemplified by the results set forth in the specification. In particular, Seidel (Theriogenology, 1997; see abstract) teaches that fourteen of 17 calves (82%) born from sex-sorted sperm were of the selected sex. The specification does not provide any examples in which spermatozoa were sorted to rates up to 100%. The prior art of Rens (US Patent 5,985216, issued 1999) does teach that bovine sperm can be sorted to purities of about 90%. Rens also teaches that under some conditions, porcine sperm could be sorted to a purity of 92% for sperm bearing the Y chromosome. However, there is no specific guidance provided in the specification for how one may

accomplish the sexing of sperm to achieve purity rates of 95%, 99% or 100% in bovine and other non-bovine mammals. It is unpredictable as to whether one of skill in the art could sort sperm from these mammals at purity rates of above 90%. The unpredictability of sorting sperm to high levels of purity, including purity levels above 90% is supported by the teachings in the art. For example, Fugger (1999; cited in the IDS) teaches that the ability to effectively sort sperm cells varies with species as a function of the shape of the sperm and the magnitude of difference in DNA content between X and Y chromosomes. Additionally, Johnson (1992, page 13; cited in the IDS) teach the difference in DNA content between X and y chromosome bearing sperm for several organisms, including turkey (0% difference), human (2.9% difference) and rabbit (3% difference). Johnson also reports that rabbit sperm were sorted to purities of 86% for X-chromosome bearing sperm and 81% for Y-chromosome bearing sperm. The specification has not taught that a representative number of non-human mammals have sperm of an acceptable shape and having an acceptable difference in the DNA content of their X and Y chromosomes to allow for the sorting of sperm at levels of more than 60, 70, 80 or 90%. There are no teachings in the prior art as to how to overcome the problems associated with a lack of difference in the DNA content between X and Y-chromosome bearing sperm or the challenges imposed by the shape, morphology and heterogeneity of sperm. The specification does not provide sufficient guidance as to how to sort sperm from non-bovine, non-porcine mammals to purity levels of 90% or above or how to sort sperm from bovine and porcine animals to up to 100% purity. It is unpredictable as to what methodologies should be employed to achieve these high

purity levels and in the absence of specific guidance provided by the specification or prior art, undue experimentation would be required to achieve these purity levels.

For the reasons set forth above and in view of the high level of unpredictability in the art and the lack of specific guidance provided in the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

Response to arguments:

In the response, Applicants traverse this rejection by arguing that the claims need not recite factors where one of ordinary skill would consider those factors to be obvious. However, the factors to which Applicants are referring are not considered to be obvious in the context of the claims. The claims are not generically drawn to methods of artificial insemination. But, rather are drawn to methods of artificial insemination in which sperm are sorted at a rate of 1200 sorts/second (a sort rate that applicants argue significantly damages sperm cells), an insemination sample is utilized which is about one half of a typical insemination sample (i.e. a significantly reduced quantity of sperm is used for the insemination process), and success rates are achieved which are from at least 35% to 90% of that obtained with a typical insemination sample (i.e., including a sample of unsorted sperm). Applicants have asserted that it is highly unexpected that one could obtain the claimed success rates using low dosages (half the "typical" sperm dosage). It is asserted, for example, that the sperm cells are highly sensitive, that sperm from each type of organism may respond differently to different chemical environments (e.g., HEPES solution versus Citrate solution), that sorting, handling, and freezing process damage sperm, and that it is extremely difficult to obtain sufficient quantities of

sorted sperm that are not damaged and which can be used for successful artificial insemination procedures. Yet, Applicant's response now asserts that the means for overcoming these problems are all obvious. That is, it is obvious that the methodology used for bovines can also be used for any mammal including rats, pandas, monkeys, whales etc; that success rates of up to 90% of that obtained with unsorted sperm can be obtained using samples of half the quantity of sorted sperm in any mammal; that any sorting device is sufficient or can be created by routine experimentation; that any sheath fluid may be utilized; that any collection medium may be utilized; and that any collection device may be employed. Applicants response does not specifically address why each of these parameters are obvious and does not provide evidence to support a conclusion that it is well within the skill of the art to select the appropriate parameters that will allow the ordinary artisan to practice the claimed invention in any manner to obtain 90% success rates using sperm samples half that of a typical insemination dosage. The specification does not provide sufficient guidance as to which particular combinations of parameters/factors may be employed to obtain the success rates recited in the claims. For instance, the specification does not exemplify that sperm from non-bovine mammals have been successfully sorted using the methodology set forth in Example 1 to achieve success rates of up to 90%. Alternatively, there are no teachings in the specification as to specific modifications of the method of example 1 which should be made to accomplish successful artificial inseminations using sperm samples obtained from, e.g., giraffes, elephants, bears etc.

Applicants assert that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. However, in the present situation, the scope of the claims does not bear a reasonable correlation to the scope of enablement. The specification provides an example of using bovine sperm for sorting and artificial insemination methods in which an 80% success rate is achieved. The specification provides no examples in which a success rate of at least 90% is achieved. No examples are provided in the specification in which at least 90% success rates were achieved with non-bovine mammals. As set forth in the rejection, it is highly unpredictable as to whether such high success rates could be obtained with bovine or any other mammal, particularly using low dosages of sorted sperm. Again, it is noted that Cran teaches that 0/18 ewes inseminated with low doses of X sperm lambed. In a second study by Cran , 0/5 ewes inseminated with low dose Y sorted sperm lambed, and only 4/25 inseminated with low dose X sorted sperm lambed. The specification teaches only one particular set of conditions – i.e., the conditions set forth in Example 1 - that were shown to be effective for achieving success rates with low dose sex-sorted sperm comparable to success rates achieved using a typical high dosage, nonsorted insemination sample. Sufficient guidance is not provided in the specification as to how to modify the conditions set forth in Example 1 and obtain a success rate that is at least about 90% of the success rate achieved with typical insemination samples for any non-human mammal.

It is argued that the specification teaches using a 2.9% sodium citrate solution for the sheath fluid and teaches that the sheath fluid can be adjusted so that it imposes less stress upon the cells. However, the specification does not exemplify a representative number of sheath fluids that can be used with any mammalian sperm and still protect the sperm from the stresses of sorting at 1200 sorts/sec in order to allow for insemination success rates with half the quantity of sperm that are of at least 90% that obtained with a typical insemination sample. The specification has asserted that the successful use of HEPES with equine is unexpected. In view of the fact that the specification acknowledges that sperm from different organisms having varying levels of sensitivity and responses to their chemical environment, the specification has not provided sufficient guidance as to how to predictably identify additional solutions that would be useful for the sheath fluid or collection fluid, while obtaining the success rates set forth in the present claims.

Applicants argue that if one can anticipate how a change will effect the claimed invention, then there is predictability in the art. However, the specification has not in fact taught how the extensive number of factors and parameters encompassed by the invention will effect the claimed subject matter. How will using HEPES buffer or citrate buffer with panda sperm affect the survival of this sperm and ability to use this sperm to obtain success rates of about 90% that of a typical insemination sample? How will using a flow cytometer at any pressure and at rates of 1200 sorts/second effect the ability of a monkey sperm sample to obtain success rates of at least about 90% that of a typical insemination sample? How will using any extender or an extender containing 1% or 2%

or 10% egg yolk effect the ability to inseminate whales and obtain success rates of at least 90%? How will using any collection container and any collection solution effect the survival of sperm from any mammal and effect the ability to use half the quantity of the resulting sperm to inseminate animals at success rates of at least 90% that of a typical insemination sample?

Most importantly, it is emphasized that the specification has provided only one example – that set forth in Example 1 – in which success rates of 80% were achieved for bovine sperm. The specification has not established that a wide variety of conditions can be used to sort bovine sperm and obtain comparable or higher success rates (of at least 90%). Further, the specification has not established that a wide variety of conditions can be used or obtained by routine experimentation to allow for the sorting of sperm from non-bovine mammals in order to obtain success rates from 35%, 41%, 50%, or at least 90% of that obtained with a typical insemination sample. Accordingly, it is maintained that in view of the high level of unpredictability in the art and the lack of specific guidance provided in the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

3. Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 as amended are indefinite over the recitation of "at least 35%, at least 41%, at least 50% and at least 90% of a typical insemination dosage" The specification does not clearly set forth what is intended to constitute a typical insemination dosage. It is not clear as to whether this dosage reflects that which is used for only sex-sorted sperm or the dosage used with unsorted sperm. The specification states that with respect to bovine, a low dose may be 500,000 sperm or 300,000 sperm or lower. For equine, it is stated that a low dose may be 25, 10, 5 or even one million sperm. Clearly, there is a significant degree of variability surrounding what might constitute "low dose" (e.g., 25 million versus 1 million) and there is no specific teaching in the specification or art as to what is generally accepted by practioners as a "typical insemination dosage" with respect to bovine, equine and other members of the broadly claimed genus of nonhuman mammals. Thereby, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Response to arguments:

In the response, Applicants argue that it is merely a matter of routine experimentation to determine what constitutes a typical insemination dosage. This argument has been fully considered but is not found persuasive. If the artisan needs to perform an experiment in order to determine the typical dosage, then clearly what constitutes a "typical dosage" is not known and defined in the art. The term "typical" means that which is commonly encountered or the average. If one does not know what is typical and can only obtain this information by experimentation, then the dosage

cannot be viewed as that which is commonly encountered. Further, it is not question of whether one could perform experiments to determine a dosage, but a question of whether one of skill in the art reading the claim would understand the meets and bounds of the claimed invention. If the art and specification does indicate what constitutes a typical insemination dosage, then one cannot determine the meets and bounds of the claimed subject matter.

B. Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 are indefinite over the recitation of "success levels comparable to a typical insemination dosage." There is no fixed definition in the art for what constitutes a typical insemination dosage for all nonhuman mammals and this phrase has not been clearly defined in the specification. Further, it is unclear as to what is considered to constitute "comparable levels." For example, it is unclear as to whether 60% or 70% or 80% or 90% or 95% of the control success rate would be considered to be a comparable level. Accordingly, one could not determine the meets and bounds of the claimed invention.

Response to arguments:

In the response, Applicants traverse this rejection by stating "the number of sperm cells in a typical insemination dosage is well within the skill in the art." This argument has been fully considered. However, as discussed above, the fact that one could determine a dosage to be used for artificial insemination does not mean that there is a fixed and complete definition in the art for "typical insemination dosage." Since the art does not teach what constitutes such a dosage and since such a dosage can only be determined and evaluated by each individual using their own criteria, the skilled artisan

would not be able to ascertain what is intended to be encompassed by obtaining a success level of at least 35%-90% of a typical insemination dosage.

C. Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 are indefinite over the recitation of "sensing a sex characteristic" because it is unclear as to what is intended to be encompassed by this phrase. It is unclear as to whether sensing encompasses actually determining a sex characteristic or whether the claims allow for guessing, estimating, inferring or predicting a sex characteristic based on some undefined attribute or characteristic. The term "sensing" does not clearly describe any particular process step and thereby one of skill in the art cannot determine what is intended to be encompassed by such a step.

Response to arguments:

In the response, Applicants traverse this rejection by stating that the specification teaches that sperm cells may be stained and that "sensing the degree of dye present in the sperm cells" can be used to discriminate the X and Y-bearing sperm cells. This argument has been fully considered but is not persuasive to overcome the present grounds of rejection. While the specification provides an example of how "sensing" may be performed, the specification does not provide a complete definition for what is intended to be encompassed by "sensing a sex characteristic." Again, this phrase is not clearly defined in the art and the specification and claims do not provide a definition for what is intended to be encompassed by this phrase.

D. Claims 10 and 174 are indefinite over the recitation of "time which is generally regarded as optimal for a single insemination." The specification and art do not provide

a clear and fixed definition for what would constitute the optimal time for any single insemination of any type for any nonhuman mammal. It is also unclear as to what time schedule is being referred to – e.g., the time within estrous or the time after sorting, etc. Accordingly, it is unclear as to what would constitute the time at which insemination is to occur.

Response to arguments:

In the response, Applicants traverse this rejection by stating that techniques are known in the art for synchronizing estrous and that an optimal time for insemination is known. It is argued that one can perform routine experimentation to determine the optimal time for insemination. These arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. The rejection is NOT premised on the fact that one of skill in the art would not know how to perform an experiment to determine a time at which insemination may occur. Rather, the rejection is based on the fact that there is not an art recognized definition for what constitutes "a time generally regarded as optimal for a single insemination." If one needs to perform an experiment to determine a time point, then this time point necessarily is not one that is "generally regarded as optimal." A time point obtained by individual researches and evaluated based on any criteria selected by the researchers is not considered to be a generally accepted time. Accordingly, the rejection is maintained because the skilled artisan would not be able to determine what is intended to be encompassed by the recitation of a "time which is generally regarded as optimal for a single insemination."

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

E. Claims 1, 5-12, 16, 17, 19-29, and 165-167, 169, 170, 172-183 and 185 are indefinite over the recitation of "separating nonhuman sperm cells based upon said sex characteristic and a rate of at least 1200 sorts per second." The claims recite only a general step of separating sperm, but do not recite that separation is accomplished by sorting the sperm. Accordingly, it is unclear as to how the recitation of "a rate of at least 1200 sorts per second" relates to the remainder of the claims.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103□ and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-12, 16, 17, 25, 28, 165, 167, 169-170, 172-183 and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1996) in view of Rens (U.S. Patent No. 5,985,216).

Seidel teaches methods for making bovine mammals comprising sorting sperm cells according to sex using flow cytometry wherein the sperm cells are sorted to purity rates of about 90%, establishing an insemination sample, inserting a low dosage (1-2 X 10^5 in .1 ml) of sorted sperm cells into the uterine horns of the female bovine after the onset of estrus; and fertilizing the eggs of the bovine so as to produce at least one offspring of the desired sex. Seidel teaches that 11 of 22 females inseminated with sperm cooled to 5C during shipping were pregnant at 8 weeks. In view of the teachings in the specification, this is considered to be a success level comparable to a typical insemination dosage. The sperm were deposited deep in the uterine horn ipsilateral to the ovary with the largest follicle being determined by ultrasound.

Seidel does not specify the rate of sorting and specifically does not teach sorting sperm at rates of 1200 sorts/second or operating a flow cytometer at 5-50 KHz.

Rens teaches a method of high speed flow cytometry for sorting sperm. In the method of Rens (see columns 4-6), a sample of sperm is obtained from a male mammal, the sperm is stained with Hoeschst 33342 dye in order to distinguish between viable and nonviable sperm (column 5, lines 4-10), the sperm are sorted in a high speed flow cytometer using a nozzle that forms a stable droplet containing each individual sperm cell (column 2, lines 23-32), the sperm are sorted according to their sex characteristics and isolated populations of X- and Y-chromosome bearing sperm are

collected. Rens teaches sampling rates of 500 sperm/second and 2000 sperm/second (column 6). Further, the nozzle allowed for sample rates up to at least 15,000 sperm/sec (column 4, lines 29-31). Rens states that the "high level of performance is beneficial for efficient sperm sorting." Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel so as to have used sorting rates of about 500 sperm/sec or 1200 sperm/second in order to have allowed for the faster sorting of sperm so as to have provided adequate quantities of sex-sorted samples that could be used for the insemination process.

Rens does not specify operating the high speed cell sorter at 5-50 KHz. However, methods for sorting sperm using high speed cell sorters were well known in the art at the time the invention was made and the parameters which would effect the sorting process were also well known. To determine the optimum conditions for performing a method step is well within the skill of the art. As discussed in MPEP 2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the optimum conditions for operating the flow cytometer, and thereby to have operated the flow cytometer within a range of 5-50 KHz depending on the rate of sorting, type of sperm, etc, in order to have provided the most effective means for sorting the sperm.

Rens does not specify the size of the collection container. However, it would have been well within the skill of the art at the time the invention was made to have selected a collection container of an appropriate width in order to have prevented damaging the sperm since Rens does teach the criticality of the dimensions of the sorting device and the orientation of the sperm within the sorting device in order to maintain sperm viability (see, for example, column 3).

With respect to claims 5, 7, 9, 11 and 12, Seidel does not teach insemination both ipsi and contra-lateral within the uterine horns.

However, Seidel (1995) teaches ipsilateral and contra-lateral insemination of low dose semen into females. The reference teaches that pregnancy rates were nearly identical for ipsilateral and contra-lateral insemination.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (1996) so as to have performed the insemination procedure by inserting the semen both ipsi and contra-lateral into the uterine horns because this would have provided an equally effective means for inseminating female bovine.

Response to arguments:

In the response, Applicants traverse this rejection by arguing that Rens does not discuss the particular sample rate at which the sperm were sorted. It is argued that "merely because the solution to a substantial problem appears simple in hindsight does not make it obvious." The response states that "(t)he current case teaches the discovery that a significant source of damage to sperm cells is by impact with the collection

container into which they are collected." It is asserted that because Rens does not disclose the problem of cells being damaged by contact with the container, one skilled in the art cannot rely on the teachings of Rens.

Applicants arguments have been fully considered but are not sufficient to overcome the present grounds of rejection. It is noted that the present claims do not require the use of a special collection device which would reduce damage to the collected sperm. Thereby, it is unclear as to how Applicant's arguments regarding the criticality of the collection device relate to the present claims. Applicant's response appears to indicate that the asserted levels of sperm dosages and success rates obtained by sorting at 1200 sorts/second can only be achieved using the special collection device discussed at pages 24-28 of the specification. If the method of the present invention can only be performed with this special collection container, then the claims should be amended to include the limitations of the collection container (i.e., a container having an inner diameter of at least 15 millimters and which matches the geometry of the stream). Further, at the time the invention was made, the sensitivity of sperm to sorting and handling processes was well known in the art. The response itself cites page 3 of the specification as teaching "(i)t has always been known that the sperm themselves are extremely delicate cells." Applicants have not provided any evidence to show that the only means for overcoming this sensitivity is by using the disclosed special collection container. The Seidel reference teaches collection of the sorted sperm into an extender containing homologous seminal plasma and other methodologies that are known in the art to protect sorted sperm. In the absence of evidence to the

contrary, the methodologies known in the art for protecting sorted sperm and the methodologies utilized by Seidel and Rens are expected to have been sufficient in order to have allowed the artisan to have practiced the sorting method at rates of 1200 sorts/second. Applicants arguments do not replace evidence and the arguments present in the response are not sufficient to establish that the combined prior art does not enable methods in which sorting is performed at rates of 1200 sorts/second.

5. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1996) in view of Rens, as set forth above, and further in view of Seidel (Theriogenology (1994) 41: 168).

The teachings of Seidel (1996) and Rens are presented above. The combined references do not teach superovulating the females prior to insemination.

Seidel (1994) teaches methods for stimulating superovulation in cows. In the method of Seidel, cows are treated twice a day at 12 hour intervals with injections of 6, 6, 4, 4, 2, 2, 2, and 2 mg FSH and given three dosages of prostaglandin of 25 mg and 12.5 mg PGF-2-alpha on days 6 and 7, respectively, of FSH treatments. The superovulation treatment is initiated starting between days 9 and 14 of the estrous cycle.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel so as to performed the surgical insemination procedure on females that were superovulated and synchronized using the FSH/PGF-2-alpha treatment methods as disclosed by Seidel (1994) in order to have achieved the benefit of providing a more effective and convenient means of

insemination since the females could then be inseminated at the most optimal time during estrous and the timing of the insemination procedure could be scheduled to correspond with the collection and sorting of sperm.

Response to arguments:

In the response, Applicants traverse this rejection for the same reasons as set forth in paragraph 5 above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

6. Claim 166 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1996) in view of Rens, as set forth above, and further in view of Rath (Theriogenology (1997) 47: 75-800; cited in the IDS) and Seidel (1995; cited in the IDS).

The teachings of Seidel and Rens are presented above. The combined references do not specify the solution into which the sperm cells are collected and thereby do not teach collecting the sorted sperm in a citrate solution containing about 6% egg yolk.

However, Rath (page 796) teaches collecting sex-sorted sperm into a collection media composed of TEST extender containing 2% hen egg yolk. Thus, Rath teaches the concept of collecting sperm sorted cells into a sperm extender medium. Additionally, Seidel (1995) teaches extending sperm in Cornell Universal Extender which is known to contain citrate and egg yolk. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (1996) so as to have collected the sperm in an extender comprising a citrate solution and egg yolk in order to have sorted the sperm into a medium that would help

to preserve the sperm and/or which could be used for subsequently freezing of the sperm.

Response to arguments:

In the response, Applicants traverse this rejection for the same reasons as set forth in paragraph 5 above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

7. Claims 1, 5-12, 16, 17, 25, 28, 29, 165, 166, 167, 169, 170, 172-183 and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1997) in view of Rens (U.S. Patent No. 5,985,216).

Seidel (pages 1257-1258 – "Experiment 2") teaches methods for making bovine mammals comprising sorting sperm cells according to sex using flow cytometry wherein the sperm cells are sorted to purity rates of about 90%, establishing an insemination sample, inserting a low dosage (1-2 X 10^5 in .1 ml) of sorted sperm cells into the uterine horns of the female bovine after the onset of estrus; and fertilizing the eggs of the bovine so as to produce at least one offspring of the desired sex. Seidel (Table 1) teaches that 50% of the females inseminated with 2.5 X 10^5 sperm became pregnant. In view of the teachings in the specification, this is considered to be a success level comparable to a typical insemination dosage. The sperm were deposited deep in the uterine horn ipsilateral or contra-lateral to the ovary with the largest follicle being determined by ultrasound.

Seidel does not teach sorting sperm at rates of 500 or 1200 sorts/second or operating a flow cytometer at 5-50 KHz.

Rens teaches a method of high speed flow cytometry for sorting sperm. In the method of Rens (see columns 4-6), a sample of sperm is obtained from a male mammal, the sperm is stained with Hoeschst 33342 dye in order to distinguish between viable and nonviable sperm (column 5, lines 4-10), the sperm are sorted in a high speed flow cytometer using a nozzle that forms a stable droplet containing each individual sperm cell (column 2, lines 23-32), the sperm are sorted according to their sex characteristics and isolated populations of X- and Y-chromosome bearing sperm are collected. Rens teaches sampling rates of 500 sperm/second and 2000 sperm/second (column 6). Further, the nozzle allowed for sample rates up to at least 15,000 sperm/sec (column 4, lines 29-31). Rens states that the "high level of performance is beneficial for efficient sperm sorting." Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel so as to have used sorting rates of about 500 sperm/sec or 1200 sperm/second in order to have allowed for the faster sorting of sperm so as to have provided adequate quantities of sex-sorted samples that could be used for the insemination process.

Rens does not specify operating the high speed cell sorter at 5-50 KHz. However, methods for sorting sperm using high speed cell sorters were well known in the art at the time the invention was made and the parameters which would effect the sorting process were also well known. To determine the optimum conditions for performing a method step is well within the skill of the art. As discussed in MPEP 2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

In re Aller, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the optimum conditions for operating the flow cytometer, and thereby to have operated the flow cytometer within a range of 5-50 KHz depending on the rate of sorting, type of sperm, etc, in order to have provided the most effective means for sorting the sperm.

Rens does not specify the size of the collection container. However, it would have been well within the skill of the art at the time the invention was made to have selected a collection container of an appropriate width in order to have prevented damaging the sperm since Rens does teach the criticality of the dimensions of the sorting device and the orientation of the sperm within the sorting device in order to maintain sperm viability (see, for example, column 3).

Seidel does not teach insemination both ipsi and contra-lateral within the uterine horns. However, Seidel does teach ipsilateral and contra-lateral insemination of low dose semen into females. Additionally, Seidel teaches that pregnancy rates were nearly identical for ipsilateral and contra-lateral insemination.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel so as to have performed the insemination procedure by inserting the semen both ipsi and contra-lateral into the uterine horns because this would have provided an equally effective means for inseminating female bovine.

Response to arguments:

In the response, Applicants traverse each of the rejections over Seidel (1997). Applicants state that they disagree with the rejection. However, the response does not present any specific arguments as to why the rejection is not proper.

Applicants state that a 132 declaration has been filed which should be sufficient to overcome the present invention. The response refers to a 132 declaration filed in parent application 09/448,643 and attached to the response as Exhibit A. This declaration has been fully considered but is not sufficient to remove the Seidel reference as prior art. The Declaration states that the Dr. Seidel is the inventor of "the invention recited by claims 124-141" of application 09/448,643. It is stated that the co-authors of the Seidel reference were not inventors of the subject matter of '643 because these authors worked under Dr. Seidel's direction.

However, the Declaration is not sufficient to remove the Seidel reference as prior art to the present invention because the Declaration does not address the subject matter of the present invention. The Declaration does not establish the role of the co-authors with respect to the presently claimed subject matter. Further, the Declaration does not address the fact that the present co-inventors Lisa Herickhoff and John Schenk are not listed on the recited reference. In summary, the Declaration does not sufficiently explain the relationship of each of the present inventors to the cited reference and to the currently claimed subject matter, nor does the Declaration sufficiently explain the relationship of each of the co-authors, other than Dr. Seidel, to the presently claimed subject matter. Accordingly, the Declaration is not sufficient to remove the Seidel (1997) reference as prior art.

8. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1997) in view of Rens, as set forth above, and further in view of Seidel (Theriogenology (1994) 41: 168).

The teachings of Seidel (1997) are presented above. Seidel does not teach superovulating the females prior to insemination.

Seidel (1994) teaches methods for stimulating superovulation in cows. In the method of Seidel, cows are treated twice a day at 12 hour intervals with injections of 6, 6, 4, 4, 2, 2, 2, and 2 mg FSH and given three dosages of prostaglandin of 25 mg and 12.5 mg PGF-2-alpha on days 6 and 7, respectively, of FSH treatments. The superovulation treatment is initiated starting between days 9 and 14 of the estrous cycle.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (1997) so as to performed the surgical insemination procedure on females that were superovulated and synchronized using the FSH/PGF-2-alpha treatment methods as disclosed by Seidel (1994) in order to have achieved the benefit of providing a more effective and convenient means of insemination since the females could then be inseminated at the most optimal time during estrous and the timing of the insemination procedure could be scheduled to correspond with the collection and sorting of sperm.

Response to arguments:

Applicants traversal of this rejection is fully addressed in paragraph 7 above.

9. Claim 166 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seidel (1997) in view of Rens, as set forth above, and further in view of Rath (Theriogenology (1997) 47: 75-800; cited in the IDS) and Seidel (1995; cited in the IDS).

The teachings of Seidel (1997) and Rens are presented above. Seidel does not teach collecting the sorted sperm into a citrate solution containing about 6% egg yolk.

However, Rath (page 796) teaches collecting sex-sorted sperm into a collection media composed of TEST extender containing 2% hen egg yolk. Thus, Rath teaches the concept of collecting sperm sorted cells into a sperm extender medium. Additionally, Seidel (1995) teaches extending sperm in Cornell Universal Extender which is known to contain citrate and egg yolk. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seidel (1996) so as to have collected the sperm in an extender comprising a citrate solution and egg yolk in order to have sorted the sperm into a medium that would help to preserve the sperm and/or which could be used for subsequently freezing of the sperm.

Response to arguments:

Applicants traversal of this rejection is fully addressed in paragraph 7 above.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5-12, 16-22, 24-29, 165-184 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent 6,071,689 in view of Seidel (1996) or Seidel (1997). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '689 are inclusive of methods for producing a nonhuman mammal wherein the methods comprise creating superovulation in a female mammal to produce at least two eggs; determining the sex of sperm cells from a male mammal and sorting the sperm cells according to sex; inserting at least a portion of the sperm cells into the uterus of said female mammal; and fertilizing a plurality of said eggs to produce multiple sexed embryos. The instant claims and the claims of '689 are further inclusive of methods in which the sperm cells are sorted by high speed flow cytometry wherein a sheath fluid is created which contains 2.9% sodium citrate, methods in which the sheath fluid contains a HEPES buffered medium, methods in which sorting is performed at rates above 500 sorts/second and methods in which a low dose of sperm cells is utilized. The claims of '689 do not recite the use of an insemination sample having a low number of sorted sperm that can be used to fertilize a nonhuman mammal at success levels comparable to a typical insemination dosage. However, Seidel (1996) and Seidel (1997) each teach methods

for producing bovine mammals comprising sorting sperm cells according to sex using flow cytometry wherein the sperm cells are sorted to purity rates of about 90%, establishing an insemination sample, inserting a low dosage (1-2 X 10^5 in .1 ml) of sorted sperm cells into the uterine horns of the female bovine after the onset of estrus; and fertilizing the eggs of the bovine so as to produce at least one offspring of the desired sex. The references each teach that insemination with low dose sorted sperm cooled to 5C during shipping occurred at a frequency of about 50%. In view of the teachings in the present specification, this is considered to be a success level comparable to a typical insemination dosage. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of '689 so as to have used the low doses of sperm taught by Seidel (1996 or 1997) in order to have provided an effective means for producing bovine of a selected sex.

Response to Arguments:

In the response, Applicants state that they disagree with the nonstatutory double patenting rejections. Applicants state that they are, however, willing to file a terminal disclaimer to expedite prosecution.

Applicants comments have been fully considered. Applicant's response does not specifically provide reasons for traversing this rejection. Further, the response does not include a terminal disclaimer. It is noted that the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained for the reasons of record and are made final.

11. Claims 1, 2, 5-12, 16-29, 165-184 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-45 of U.S. Patent 6,524,860 in view of Seidel (1996) or Seidel (1997). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '860 are inclusive of methods for producing a nonhuman mammal wherein the methods comprise establishing a cell source which supplies cells to be sorted, chemically coordinating a sheath fluid to create a sheath fluid environment for said cells wherein the sheath fluid is coordinated with both the pre-sort and post-sort environment, separating the sperm cells according to sex; inserting at least a portion of the sperm cells into the uterus of a female nonhuman mammal; and fertilizing a plurality of said eggs to produce a nonhuman mammal. The instant claims and the claims of '860 are further inclusive of methods in which the sperm cells are sorted by high speed flow cytometry wherein a sheath fluid is created which contains 2.9% sodium citrate, methods in which the sheath fluid contains a HEPES buffered medium, methods in which sorting is performed at rates above 500 sorts/second, methods in which the sperm are stained using 38uM, methods in which the sperm are collected in wide collection tubes, and methods in which a low dose of sperm cells is utilized. The claims of '860 do not recite the use of an insemination sample having a low number of sorted sperm that can be used to fertilize a nonhuman mammal at success levels comparable to a typical insemination dosage. However, Seidel (1996) and Seidel (1997) each teach methods for producing bovine mammals comprising sorting sperm cells according to sex using flow cytometry wherein the sperm

cells are sorted to purity rates of about 90%, establishing an insemination sample, inserting a low dosage (1-2 X 10^5 in .1 ml) of sorted sperm cells into the uterine horns of the female bovine after the onset of estrus; and fertilizing the eggs of the bovine so as to produce at least one offspring of the desired sex. The references each teach that insemination with low dose sorted sperm cooled to 5C during shipping occurred at a frequency of about 50%. In view of the teachings in the present specification, this is considered to be a success level comparable to a typical insemination dosage. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of '860 so as to have used the low doses of sperm taught by Seidel (1996 or 1997) in order to have provided an effective means for producing bovine of a selected sex.

Response to Arguments:

In the response, Applicants state that they disagree with the nonstatutory double patenting rejections. Applicants state that they are, however, willing to file a terminal disclaimer to expedite prosecution.

Applicants comments have been fully considered. Applicant's response does not specifically provide reasons for traversing this rejection. Further, the response does not include a terminal disclaimer. It is noted that the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained for the reasons of record and are made final.

12. Claims 1, 2, 5-12, 16-22, 24-29, 165-184 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-18 of U.S. Patent 6,372,422 in view of Seidel (1996) or Seidel (1997). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '422 are inclusive of methods for producing a nonhuman mammal wherein the methods comprise establishing a cell source which supplies cells to be sorted, separating sperm cells according to sex; inserting at least a portion of the sperm cells into the uterus of a female nonhuman mammal that has been superovulated and fertilizing a plurality of said eggs to produce a nonhuman mammal. The instant claims and the claims of '422 are further inclusive of methods in which the sperm cells are sorted by high speed flow cytometry wherein a sheath fluid is created which contains 2.9% sodium citrate, methods in which the sheath fluid contains a HEPES buffered medium, methods in which sorting is performed at rates above 500 or 12000 sorts/second, methods in which the sperm are collected in wide collection tubes, and methods in which a low dose of sperm cells is utilized. The claims of '422 do not recite the use of an insemination sample having a low number of sorted sperm that can be used to fertilize a nonhuman mammal at success levels comparable to a typical insemination dosage. However, Seidel (1996) and Seidel (1997) each teach methods for producing bovine mammals comprising sorting sperm cells according to sex using flow cytometry wherein the sperm cells are sorted to purity rates of about 90%, establishing an insemination sample, inserting a low dosage (1-2 X 10^5 in .1 ml) of sorted sperm cells into the uterine horns of the female bovine after the onset of estrus; and fertilizing the eggs of the bovine so as to produce at least one offspring of the desired sex. The references each teach that insemination with low dose sorted

sperm cooled to 5C during shipping occurred at a frequency of about 50%. In view of the teachings in the present specification, this is considered to be a success level comparable to a typical insemination dosage. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of '422 so as to have used the low doses of sperm taught by Seidel (1996 or 1997) in order to have provided an effective means for producing bovine of a selected sex.

Response to Arguments:

In the response, Applicants state that they disagree with the nonstatutory double patenting rejections. Applicants state that they are, however, willing to file a terminal disclaimer to expedite prosecution.

Applicants comments have been fully considered. Applicant's response does not specifically provide reasons for traversing this rejection. Further, the response does not include a terminal disclaimer. It is noted that the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained for the reasons of record and are made final.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
April 18, 2005

CARLA J. MYERS
PRIMARY EXAMINER